Timed inhibition of p38MAPK directs accelerated differentiation of human embryonic stem cells into cardiomyocytes.

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Public Summary:

Scientific Abstract:
BACKGROUND AIMS: Heart failure therapy with human embryonic stem cell (hESC)-derived cardiomyocytes (hCM) has been limited by the low rate of spontaneous hCM differentiation. As others have shown that p38 mitogen-activated protein kinase (p38MAPK) directs neurogenesis from mouse embryonic stem cells, we investigated whether the p38MAPK inhibitor, SB203580, might influence hCM differentiation. METHODS: We treated differentiating hESC with SB203580 at specific time-points, and used flow cytometry, immunocytochemistry, quantitative real-time (RT)-polymerase chain reaction (PCR), teratoma formation and transmission electron microscopy to evaluate cardiomyocyte formation. RESULTS: We observed that the addition of inhibitor resulted in 2.1-fold enrichment of spontaneously beating human embryoid bodies (hEB) at 21 days of differentiation, and that 25% of treated cells expressed cardiac-specific alpha-myosin heavy chain. This effect was dependent on the stage of differentiation at which the inhibitor was introduced. Immunostaining and teratoma formation assays demonstrated that the inhibitor did not affect hESC pluripotency; however, treated hESC gave rise to hCM exhibiting increased expression of sarcomeric proteins, including cardiac troponin T, myosin light chain and alpha-myosin heavy chain. This was consistent with significantly increased numbers of myofibrillar bundles and the appearance of nascent Z-bodies at earlier time-points in treated hCM. Treated hEB also demonstrated a normal karyotype by array comparative genomic hybridization and viability in vivo following injection into mouse myocardium. CONCLUSIONS: These studies demonstrate that p38MAPK inhibition accelerates directed hCM differentiation from hESC, and that this effect is developmental stage-specific. The use of this inhibitor should improve our ability to generate hESC-derived hCM for cell-based therapy.